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ABSTRACT: Adductor pollicis muscle function of a 21-year-old man with genetically confirmed Brody's disease (sarcoplasmic reticulum [SR]-Ca²⁺ATPase deficiency) was investigated to study the possible effects of reduced SR-Ca²⁺ATPase activity on muscle relaxation and force production. Following maximal electrical activation of the ulnar nerve, tetanic muscle half-relaxation time was greater in the patient (246 ± 10 ms) than control subjects (97 ± 4 ms, $n = 8$). During repetitive activation, there was a similar decline in maximal shortening velocity in the patient and controls, indicating a comparable reduction in cross-bridge cycling rate. The finding that the slowing of relaxation was greater in the patient (329 ms versus 138 ± 20 ms) suggests that there was a further reduction of SR-Ca²⁺ATPase activity in the patient's muscle during fatigue. Following a voluntary contraction, involuntary activity of the antagonist muscles facilitated force decline and masked the impaired relaxation in the patient. This antagonist-induced relaxation indicates that it might be difficult to establish impaired muscle relaxation with voluntary contractions.

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MUSCLE FUNCTION IN A PATIENT WITH BRODY'S DISEASE

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Skeletal muscle contraction is triggered by Ca²⁺ release from the sarcoplasmic reticulum (SR). The binding of Ca²⁺ to troponin enables cross-bridge interaction and hence force production. During muscle activation, Ca²⁺ is pumped back continuously from the cytosol into the lumen of the SR by an adenosine triphosphate (ATP)-dependent pump (SR-Ca²⁺ATPase). Following muscle activation, relaxation is initiated by this Ca²⁺ pump, which brings the free Ca²⁺ concentration in the cytosol back to resting levels. Selective inhibition of the SR-Ca²⁺ pump might slow relaxation, as has been demonstrated in isolated mouse muscle.¹⁸ Fatiguing exercise also is frequently accompanied by a slowing of muscle relaxation. However, the cause of the slowing of muscle relaxation during fatigue remains unclear

and may in principle be due to a reduced rate of cross-bridge cycling¹⁹ or a slowed Ca²⁺ handling.^{5,8} The latter factor would include a decreased rate of Ca²⁺ removal from the sarcoplasm due to reduced activity of SR-Ca²⁺ATPase in fatigue. The purpose of the present investigation was to clarify further the physiological role of SR-Ca²⁺ATPase during muscle activity in humans, by studying muscle function in a patient with a reduced activity of the enzyme caused by a genetic defect in the SR-Ca²⁺ATPase gene. In 1969, Brody³ was the first to describe a patient with SR-Ca²⁺ATPase deficiency and impaired muscle relaxation. Recently, Odermatt et al.^{13,14} detected mutations in the ATP2A1 gene on chromosome 16p12.1–12.2 that encodes the fast-twitch isoform of SR Ca²⁺ATPase (SERCA1), in patients with Brody's disease. This permits the diagnosis to be confirmed at the genetic level. To our knowledge, the diagnosis has been confirmed with DNA techniques in only five patients worldwide. We had the opportunity to carry out exercise testing in one of these cases (patient no. 4 of Benders et al.¹ and patient F1P3 of Odermatt et al.¹³) to study the physiological role of

Abbreviations: 0.5 RT, half-relaxation time; SR, sarcoplasmic reticulum; V_{max}, maximal rate of cross-bridge cycling.

Key words: Brody's disease, SR-Ca²⁺ATPase, skeletal muscle, antagonist induced relaxation, fatigue

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SR-Ca²⁺ATPase. The main objective was to study the possible effects of reduced SR-Ca²⁺ATPase activity on relaxation rate, force production, and shortening velocity in fresh and fatigued human muscle. In the unfatigued muscle, relaxation was expected to be slower in the patient than in the healthy individuals. Cross-bridge function, however, should be unaffected by the deficiency, and force production during isometric and dynamic muscle contractions should therefore be normal in the patient. Furthermore, it was hypothesized that during repetitive activation the reduced rate of Ca²⁺ removal from the cytosol should become further impaired in the patient, and it was anticipated that this should aggravate the slowing of relaxation during fatigue.

METHODS

The patient was a 21-year-old man who had been diagnosed with Brody's disease. He is one of the five SR-Ca²⁺ATPase-deficient patients in the world in whom the genetic cause of the disease has been confirmed (patient F1P3 of Odermatt et al.¹³). A homozygous C592T mutation was found in exon 7 of the ATP2A1 gene on chromosome 16p12.1–12.2, which encodes SERCA1.¹³ Furthermore, SERCA1 activity in quadriceps muscle samples of this patient was reduced to about 40% of normal, and the patient's main problem was impaired muscle relaxation following exercise.¹ He reported difficulties during (prolonged) walking and stair climbing, but otherwise he was healthy and had a physically demanding job requiring lifting and carrying of heavy objects.

In addition, eight healthy male subjects (20–33 years of age) took part in the experiments. The data of this group served as a reference for comparison with the patient's data. Approval of the Ethical Committee of the Vrije Universiteit was obtained, and all subjects gave informed consent.

Experimental Arrangement. The methods for stimulating the adductor pollicis, recording force, and imposing length changes are given in detail elsewhere.⁷ Briefly, the subject sat in an adjustable chair with the left forearm supinated, the hand held horizontally, and the thumb abducted and in contact with a vertical pin attached to a strain gauge mounted below the plane of the hand. The entire hand, with the exception of the thumb, was immobilized with a Perspex plate, which was tightened down onto a mould fitting into the palm.

The force transducer was attached via a lever system to a linear step motor such that linear displacement of the motor was converted into rotation of the

vertical pin around the carpometacarpal joint of the thumb. When the thumb was fully adducted, its length axis was parallel to the length axis of the index finger, and this position was defined as 0° thumb angle. Because the vertical pin of the force transducer was placed between the thumb and the index finger, the smallest thumb angle at which forces could be measured was 36°. It was possible to increase thumb angle up to 74° (maximal abduction) before anatomical limits were approached. Thus, during shortening contractions, the maximal angular displacement was 38°.

The adductor pollicis muscle was activated by percutaneous electrical stimulation of the ulnar nerve at the wrist, with constant current unidirectional square-wave pulses of 100 ms duration (Digitimer Ltd, model DS7, Welwyn Garden City, England).

Electromyogram Recordings. The electromyogram (EMG) was recorded with two pairs of self-adhering neonatal electrocardiogram (EKG) Ag-AgCl electrodes (Medi-Trace, Technomed, Beek, The Netherlands). The skin was shaved and cleaned before placing the electrodes. Two electrodes were placed on the skin over the adductor pollicis muscle (2.5 cm between the centers of the electrodes). The other pair was placed over the abductor pollicis longus and extensor pollicis brevis muscles (4.5 cm apart). The EMG signal of the latter pair will be referred to as the EMG of the abductor muscles. A silver plate (2 × 6 cm) was placed underneath the straps of the stimulation electrodes on the palmar side of the wrist and served as common-mode electrode. Correct placement of the electrodes was checked with voluntary abduction and adduction of the thumb. The EMG signals were amplified, bandpass filtered (10 Hz to 8 kHz), digitized (10 kHz), and stored on computer disk along with the force and length signal.

Experimental Procedures. During a first session, subjects were familiarized with the electrical stimulation and the other procedures. Data were collected only during a second visit. To maintain a constant muscle temperature, the subject's hand and arm were immersed in a water bath at 45°C for 30 min prior to the test. During the experiment a lamp was used to maintain skin temperature over the adductor pollicis at 36.0° ± 0.5°C, measured with a thermocouple. In two control subjects, a thermocouple was inserted in the muscle, and muscle temperature was found to vary between 35.5°C and 37.0°C during the experiment.

Force/Frequency Relationship and Relaxation. Isometric force was measured using 1-s stimulation at a 51° angle between thumb and index finger. A force/frequency relationship was established using different stimulation frequencies (1–200 Hz), the maximal force obtained at each frequency being measured. There was 2 min of rest between contractions. Muscle half-relaxation times (0.5 RT) were calculated to quantify muscle relaxation. The measurement 0.5 RT was defined as the time during which force decreased from the peak to 50% at the end of stimulation.

Force/Velocity Relationship. Single-isovelocity contractions (80 Hz stimulation frequency) were induced in the muscle in order to establish a force/velocity relationship. A force/velocity curve was constructed using isovelocity contractions at seven different angular velocities (0°/s, 76°/s, 153°/s, 229°/s, 306°/s, 382°/s, and 458°/s) applied in random order. The shortening started during the rise phase of isometric force development; the muscle was allowed to shorten at the moment that force reached a level which was “expected” during the following shortening phase. This was done so that forces were constant during the shortening phase. With a constant force, the length of the series’ elastic elements (muscle tendons) will not change, and therefore the shortening velocity of the series elastic elements will be zero. Consequently, the velocity at which the contractile elements (muscle fibers) shortened was the velocity imposed upon the entire muscle–tendon complex. The starting angle and the timing of the release after the start of stimulation were adjusted such that constancy of force was reached around the 51° thumb angle at all applied velocities. The 51° thumb angle is the optimum for force production, although it should be noted that the length/force relationship of the adductor pollicis muscle is essentially flat in the range of thumb angles used in the present study.⁷ The shortening conditions were established by trial and error in pilot experiments. Small adjustments were made for each individual. An example of an isovelocity (153°/s) shortening contraction is presented in Figure 1.

At each velocity, the passive force at 51° (thumb movement without muscle activity) was subtracted from the total force. The resulting active force (active force = total force – passive force) represents the force exerted by the contractile elements. Thus, all forces reported in this study are active forces measured at the 51° thumb angle.

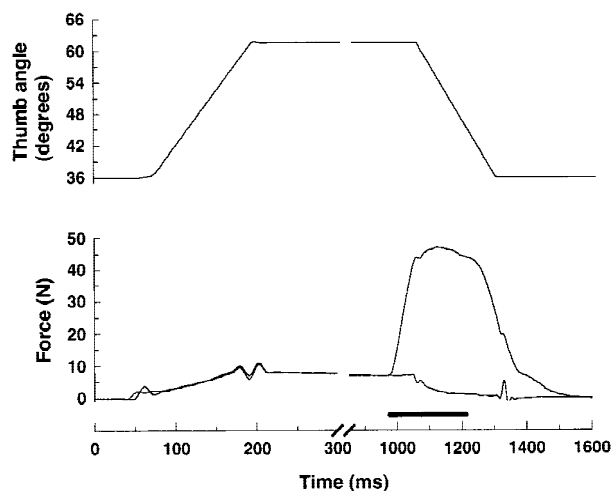


FIGURE 1. Example of an isovelocity shortening contraction at 153°/s. Following passive abduction to a 64° thumb angle (top panel), the muscle was electrically stimulated (80 Hz), as indicated by the black bar above the time axis. After a short isometric phase, during which force increased (to 44 N), the thumb was allowed to adduct at constant velocity (153°/s). This sequence was repeated without electrical stimulation, thus with a passive muscle (lower force trace). Active muscle force was obtained by subtracting the passive force from the total force at a 51° thumb angle. Note the different scaling left and right from the break in the time axis.

Muscle Fatigue. After the force/velocity measurements in the unfatigued state had been completed, a cuff around the subject’s upper arm was inflated to 200 mmHg, and the muscle was then fatigued. The adductor pollicis performed 60 isometric contractions of 240 ms duration at a 51° thumb angle. A 50-Hz stimulation frequency was used. This fatigue protocol was immediately followed by a quick series of seven randomly ordered contractions (0 to 458°/s). The entire series of isovelocity contractions in the fatigued state was completed within 20 s. Subsequently the cuff was deflated. After 6 min of rest, isometric force had recovered to $98 \pm 3\%$ of the prefatigue value. After 12 min a complete force/velocity relationship was obtained. Recovered forces of the patient and the control subjects were always within 5% of the prefatigue values at all velocities.

Original Force Traces. In several figures, original force traces of the patient are presented and compared with those of one of the healthy subjects, selected because maximal isometric force of his adductor pollicis muscle was similar to that of the patient.

Data Analysis and Statistics. At each velocity, active forces at the 51° thumb angle were used to construct force/velocity relationships (fresh and fa-

tigued) of the muscle. Data points were fitted (least squares) to a hyperbola as described by Hill.¹⁰ The results of the healthy individuals are presented as means \pm SD.

RESULTS

At the start of the experiment, the patient was instructed to maximally adduct his thumb for a few seconds and to stop squeezing on instruction of the experimenter. Although there were no obvious problems with respect to the relaxation of force (Fig. 2A) substantial EMG activity was recorded from the abductor muscles during relaxation (Fig. 2A). Even after several trials, the patient was unable to stop

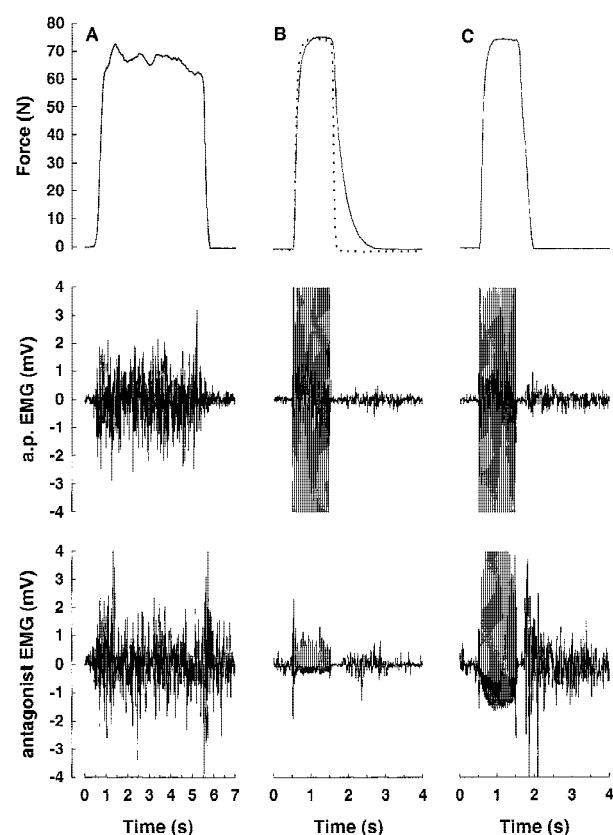


FIGURE 2. Maximal voluntary contraction of the adductor pollicis muscle in the patient. Forces (top) and EMG of the adductor pollicis (middle) and the antagonist muscles (bottom) of the patient are shown for: a 5 s maximal voluntary contraction (A), a 1-s electrically induced contraction (B), and a 1-s electrically induced contraction followed by voluntary effort in order to facilitate force relaxation (C). Relaxation in (B) clearly is impaired compared with the control subject (dotted trace); EMG signals in the patient remained (almost) silent during relaxation. Force relaxation appears to be normal in both (A) and (C). Note, however, that in both contractions there was substantial EMG activity of the antagonist muscles during relaxation.

adducting his thumb during a voluntary contraction without the use of his abductors.

When the patient's adductor pollicis was electrically stimulated, muscle relaxation was clearly impaired (Figs. 2B and 3). Figure 2B shows that during the relaxation phase, the EMG of the patient's adductor and abductor muscles was silent. In Figure 2C, the results are shown for a similar contraction as in Figure 2B, except that the patient was instructed to use his abductors immediately after cessation of the electrical pulse train in order to bring force back to baseline more quickly. In this way the patient's "natural" response following a voluntary contraction (Fig. 2A) was mimicked. Indeed, in both Figs. 2A and 2C, a fast (apparently normal) decline of force was accompanied by substantial EMG activity of the abductor muscles.

As expected, tetanic (80 Hz stimulation frequency) 0.5 RT was slower in the patient (246 ± 10 ms, mean of 4 tetani) compared with the control subjects (97 ± 4 ms; range, 89–103 ms). The slower relaxation was already visible following a twitch of the muscle (Figs. 3B and 3C). Twitch 0.5 RT was two times longer in the patient (112 ± 4 ms, mean of six twitches) compared with control values (54 ± 6 ms; range, 42–60 ms). Furthermore, the forces obtained with submaximal stimulation frequencies were higher in the patient compared with control subjects (Fig. 3). With 10 Hz stimulation (Fig. 3), forces in the patient and healthy subjects, respectively, were 69% and $21 \pm 6\%$ of maximum force (Fig. 4). The twitch/tetanic force ratio was 0.17 in the patient compared with 0.11 ± 0.01 in the controls. Consequently, the patient's force/frequency relationship was shifted to the left compared with control subjects (Fig. 4).

Due to the slow relaxation, the patient's thumb force failed to reach the baseline after the first contraction of the fatigue test (Fig. 5). Muscle relaxation in the control subjects also became considerably slower during the fatigue test. In these healthy individuals, however, force declined to baseline values between contractions up until the end of the test (Fig. 5). There was a 45% force decline in the patient's muscle (Fig. 5) compared with a decrease of $22 \pm 5\%$ in control subjects. Thus, there seems to be an increased fatigability in the patient's muscle. However, the (isometric) force obtained in the fatigue state immediately following the fatigue test (with the blood flow still occluded) was similar compared with control values (Figs. 6 and 7).

The fatigue test caused an increase in tetanic 0.5 RT of 329 ms (from 246 ms to 575 ms) in the patient and of 138 ms (from 97 ± 4 ms to 235 ± 42 ms) in

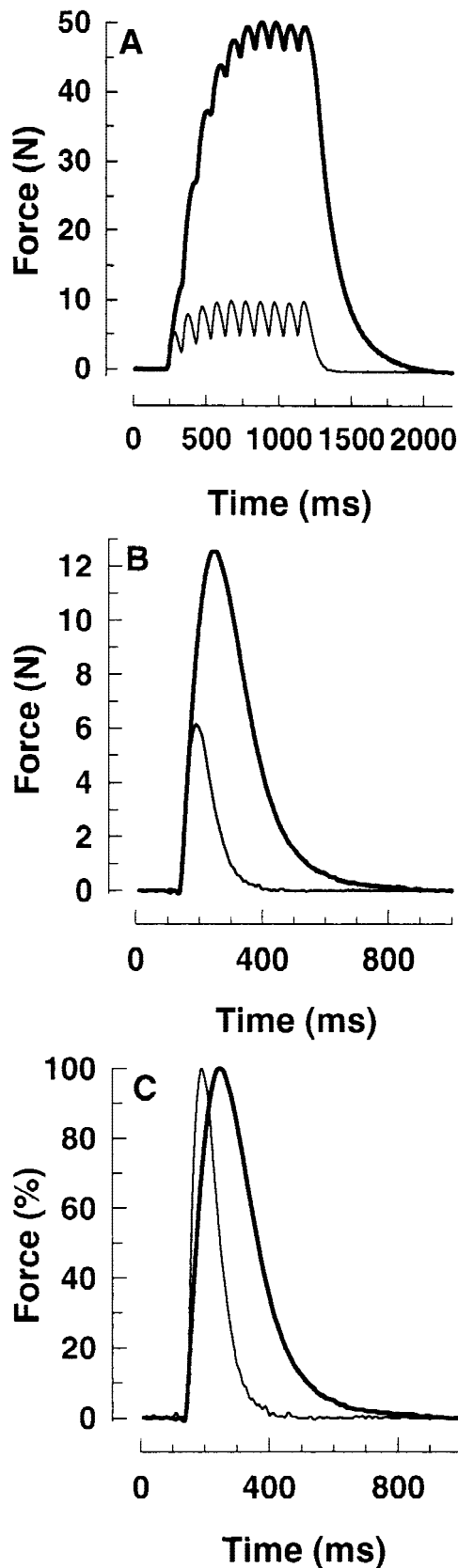


FIGURE 3. 10-Hz tetanic and twitch forces. Tetanic force (1-s contraction, 10-Hz stimulation frequency) at the 51° thumb angle (**A**) and twitch force (**B**) of the patient (bold traces) and a control subject with similar maximal thumb adduction strength (± 73 N). (**C**) Twitch forces are normalized (peak = 100%); note the much broader twitch of the patient.

controls. Examples of tetanic force signals in the fresh and fatigued adductor pollicis of the patient and a control subject are shown in Figure 6. In both the fresh and fatigued muscle, relaxation was impaired in the absence of any electrical activity of the muscle, as illustrated by the lack of EMG activity during relaxation (Fig. 6). In accordance with our hypothesis, the force-generating capacity of the muscle was apparently not impaired in the patient. Over the entire range of shortening velocities, both in the fresh and fatigued state, force of the adductor pollicis of the patient was within the range of controls. Consequently, the patient's force/velocity relationships (fresh and fatigued muscle) were similar to those of the healthy subjects (Fig. 7).

DISCUSSION

This study is the first to investigate the physiological consequences of SR-Ca²⁺ATPase deficiency for human skeletal muscle function in detail. An unexpected finding was that force quickly returned to baseline values after voluntary effort due to activation of the antagonist muscles (Fig. 2A). This phenomenon, which we designate antagonist-induced relaxation, occurred automatically, even when the

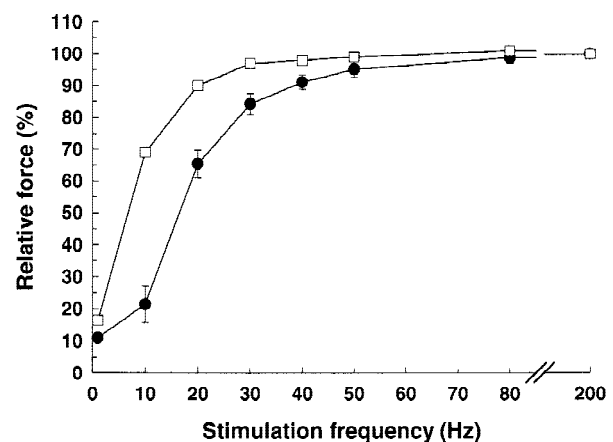


FIGURE 4. Force/frequency relationships. Maximal thumb adduction force as a function of stimulation frequency (force at 200 Hz = 100%) in the patient (open squares) and control subjects (closed circles, mean \pm SD).

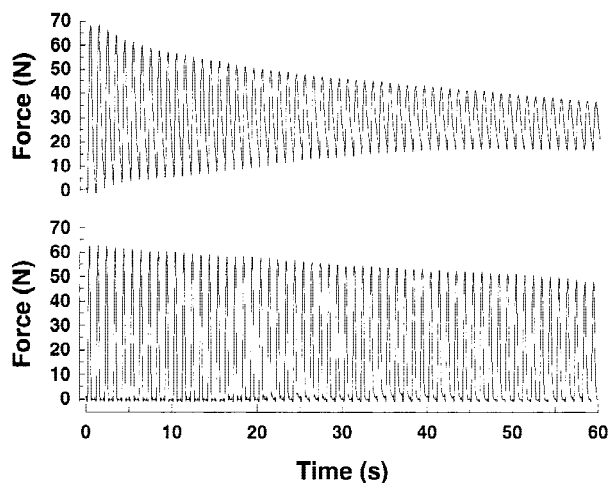


FIGURE 5. Force during repetitive isometric contractions. Original force traces during 60 isometric contractions (240 ms duration; 50 Hz stimulation frequency; one contraction each second) of the patient (top) and a control subject (bottom).

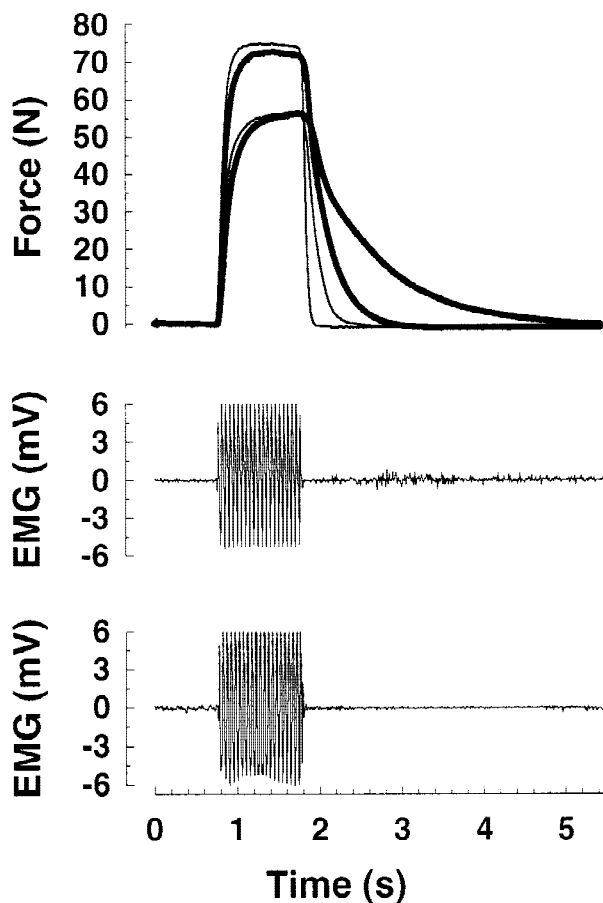


FIGURE 6. Isometric force in fresh and fatigued muscle. Isometric (1-s contractions; 80 Hz) adductor pollicis muscle force (top) of a healthy subject (thin traces) and the patient (bold traces) in the fresh and fatigued (slower relaxation) state. Electromyograph signals of the patient's adductor pollicis muscle in the fresh (middle) and fatigued (bottom) state are also shown.

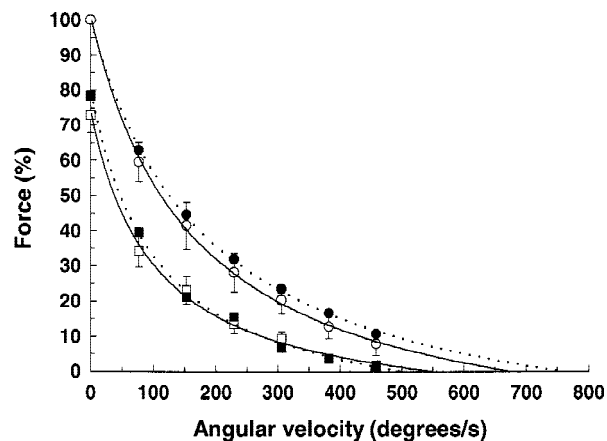


FIGURE 7. Force/velocity relationships in fresh and fatigued adductor pollicis muscle. Force as a function of angular velocity in the fresh (circles) and fatigued (squares) adductor pollicis muscle of the patient (closed symbols, dotted lines) and healthy subjects (open symbols, mean \pm SD).

patient tried hard not to use the antagonist muscles during relaxation. It is likely that antagonist-induced relaxation has become a strategy of the patient's neuromuscular system, allowing him to open his hand quickly, even though his agonist muscles are still exerting force. Although this is clearly a very functional adaptation, it will also increase the workload placed upon the shortening muscles during cyclic activities such as walking and stair climbing. During such activities, antagonist muscles have to forcefully stretch force-exerting agonist muscles. Consequently, the energy costs and metabolic changes are likely to increase during cyclic activities. Therefore, increased metabolic changes may explain the aggravation of clinical symptoms, such as an enhanced fatigability, in other SR-Ca²⁺ATPase-deficient patients during exercise.^{2-4,12,15,16,20}

With electrically induced contractions, 2.5-fold longer 0.5 RTs were found in the patient compared with healthy subjects (Figs. 2 and 6). The slower rate of relaxation probably accounts for the increased rate of fusion and the higher forces at low frequencies of stimulation (Figs. 3 and 4) in the patient's muscle. These findings are in accordance with the notion that there is a prolongation of the active state following contraction, caused by a slower re-uptake of Ca²⁺ from the sarcoplasm due to a reduced function of the SR-Ca²⁺ pump. Support for this explanation is offered by the finding that selective inhibition of the SR-Ca²⁺ pump in isolated mouse muscle fibers leads to a significant slowing of relaxation.¹⁸ However, it cannot be excluded that some other mechanism may have led to or contributed to the slowed relaxation in our patient.

It might be argued that the impaired relaxation and twitch potentiation in the patient could also be explained by an increased Ca^{2+} loading of parvalbumins, which would diminish the capacity of parvalbumins as a soluble relaxing factor following stimulation. Consequently, the free Ca^{2+} concentration following activation would remain higher in the patient's muscle, which in theory could account for the twitch potentiation and the slowed relaxation. Although there is some evidence that parvalbumins speed up muscle relaxation in cold-blooded animals at low muscle temperatures,¹¹ and to some extent also in small mammals, such as the mouse, at room temperature,¹⁸ we are unaware of studies demonstrating that parvalbumins play an important role in human muscle relaxation at 36°C. Moreover, the parvalbumin concentration in human muscle is very low compared with fast-twitch mouse muscle (<0.001 g/kg versus 4.9 g/kg, respectively⁹). Therefore, although we cannot exclude a possible role of parvalbumins in our measurements, we believe that the impaired relaxation and the twitch potentiation in our patient are the direct consequence of the reduced SR- Ca^{2+} ATPase activity.

An interesting finding was that we were unable to confirm the impaired relaxation found by Brody³ following voluntary activation of the adductor pollicis muscle in a SR- Ca^{2+} ATPase-deficient patient. Furthermore, twitch relaxation was impaired in our patient, whereas Brody³ reported a normal (63 ms) twitch 0.5 RT of the adductor pollicis muscle in his patient. Such discrepancies may have been caused by the fact that the patient investigated by Brody may not have had a defect in the SR- Ca^{2+} ATPase gene. To our knowledge, the defect in the SERCA1 gene has not been investigated at the DNA level in Brody's patient (personal communication, D.H. MacLennan). Zhang and coworkers²¹ have previously investigated at least three cases of presumed Brody's disease where no mutation could be found in the SERCA1 gene. In such patients, the explanation for the low SR- Ca^{2+} ATPase activity measured in muscle samples using biochemical methods is sought in defects in other proteins like sarcolipin, which are associated with SERCA1.¹⁴ For this reason we have chosen to investigate muscle function in a genetically confirmed case of SR- Ca^{2+} ATPase deficiency.

There are no indications in the literature that maximal force production during a single short tetanic contraction depends on SR- Ca^{2+} ATPase activity. Therefore, the patient's ability to exert force, under isometric as well as under dynamic conditions, was not expected to be affected by the disease. In-

deed, maximal isometric force and the force/velocity relationship of the patient's adductor pollicis muscle were very similar to that of the control subjects. However, because the physiological cross section of the muscles was not obtained, it cannot be excluded that the specific tension (= force/cross section) of the patient's muscle was different. Nevertheless, our findings strongly suggest that the clinical symptoms in the patient were strictly related to the deficiency in SR- Ca^{2+} ATPase and were not caused by other malfunctions at the cross-bridge level.

During the fatigue test, isometric force decreased more in the patient than in controls. This may indicate that SR- Ca^{2+} release decreased during repetitive activation of the patient's muscle. The differences in isometric force production between the patient and control subjects disappeared within seconds following the fatigue test, showing that force recovered to some extent in the deficient muscle in spite of the occluded blood flow. In the fatigued state, there was more rest between contractions than during the fatigue test, which may have improved SR Ca^{2+} loading and consequently Ca^{2+} release during the next tetanus. In addition, the higher-stimulation frequency (80 Hz) used following the test, compared with the 50 Hz applied during the test may have restored Ca^{2+} release in the patient's muscle to the level required for maximal force production under those circumstances. There may, however, be other explanations for the more pronounced decline of force in the patient's muscle during the fatigue test, such as compartmentalization of metabolites.

A leftward shift of the force/velocity relationship during repetitive activation has been found in isolated muscle and single-fiber preparations, indicating that not only isometric force production but also cross-bridge cycling rate (V_{max}) decreases during fatigue.^{6,17} The present results on human muscle support these previous findings, which suggested that a decreased cross-bridge detachment rate is an important cause for the slowing of relaxation observed during fatigue. However, V_{max} and force production decreased to similar extents in the fatigued muscle of the patient and control subjects, whereas muscle relaxation was more affected in the patient. These results indicate that the changes in cross-bridge function during fatigue were similar in the patient and control subjects. The findings also suggest that in the deficient muscle it is likely that in addition to a slowed cross-bridge detachment rate, an impaired rate of SR Ca^{2+} pumping contributed to the fatigue-induced slowing of relaxation.

CONCLUSION

Relaxation was severely prolonged in the electrically stimulated adductor pollicis muscle of a SR- Ca^{2+} -ATPase-deficient patient. Following voluntary activation, the patient used his antagonist muscles to speed up force decline (antagonist-induced relaxation). The deficiency did not affect cross-bridge function, as was demonstrated by the similar force/velocity relationships of the patient muscles and control muscles. During repetitive activation, the reduction in maximal shortening velocity, indicative for the maximal rate of cross-bridge cycling, was similar in the controls and the patient. This similarity was expected to cause a comparable slowing of relaxation in the patient and controls. However, the slowing of relaxation in the fatigued muscle of the patient was greater, which could have been due to a further reduction of SR- Ca^{2+} -ATPase activity during repetitive activation. Although the data are obtained from a single patient, the present findings confirm the generally accepted physiological role of SR- Ca^{2+} -ATPase during muscle activity.

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